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Health Effects Assessment for 1,2-Dichloroethane

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HEALTH EFFECTS ASSESSMENT FOR 1,2-DICHLOROETHANE

U.S. Environmental Protection Agency
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Environmental Criteria and Assessment Office
Cincinnati, OH 45268

U.S. Environmental Protection Agency
Office of Emergency and Remedial Response
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16. ABSTRACT

This document represents a brief, quantitatively oriented scientific summary of health effects data. It was developed by the Environmental Criteria and Assessment Office to assist the Office of Emergency and Remedial Response in establishing chemical-specific health-related goals of remedial actions. If applicable, chemical-specific subchronic and chronic toxicity interim acceptable intakes are determined for systemic toxicants, or q_1^* values are determined for carcinogens for both oral and inhalation routes.

A q_1^* was determined for 1,2-dichloroethane based on oral exposure.

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PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with 1,2-dichloroethane. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the Chemical Abstracts, TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to September, 1984. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980a. Ambient Water Quality Criteria for Chlorinated Ethanes. Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 440/5-80-029. NTIS PB 81-117400.

U.S. EPA. 1983a. Reportable Quantity for 1,2-Dichloroethane. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1984. Health Assessment Document for Ethylene Dichloride. External Review draft. Environmental Criteria and Assessment Office, Research Triangle Park, NC, OHEA. EPA-600/8-84-006A. NTIS PB84-209865.

The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, the AIS or acceptable intake subchronic, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for AIS estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure.

The AIC, acceptable intake chronic, is similar in concept to the ADI (acceptable daily intake). It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980b) for a discussion of this concept]. The AIC is route specific and estimates acceptable exposure for a given route with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for ranking reportable quantities; the methodology for their development is explained in U.S. EPA (1983b).

For compounds for which there is sufficient evidence of carcinogenicity, AIS and AIC values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1983b). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. Consequently, derivation of AIS and AIC values would be inappropriate. For carcinogens, q_1^*s have been computed based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment in proper context, the reader is referred to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates.

1,2-Dichloroethane has been shown to be carcinogenic in mice and rats following oral exposure. Existing data have not demonstrated an association between inhalation exposure and cancer in experimental animals. Human data are lacking.

U.S. EPA (1984) has computed a q_1^* of 6.9×10^{-2} $(mg/kg/day)^{-1}$ for 1,2-dichloroethane using data on the incidence of hemangiosarcomas in male rats.

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
AIC	Acceptable intake chronic
AIS	Acceptable intake subchronic
CS	Composite score
FEL	Frank-effect level
GI	Gastrointestinal
GLC	Gas-liquid chromatography
i.p.	Intraperitoneal
LOAEL	Lowest-observed-adverse-effect level
MED	Minimum effective dose
NADPH	Nicotinamide adenine dinucleotide phosphate (reduced form)
NOEL	No-observed-effect level
PCB	Polychlorinated biphenyl
RV_d	Dose-rating value
RV_e	Effect-rating value
SRBC	Sheep red blood cells
STEL	Short-term exposure limit
TLV	Threshold limit value
TWA	Time-weighted average

1. ENVIRONMENTAL CHEMISTRY AND FATE

The relevant physical and chemical properties and environmental fate of 1,2-dichloroethane (CAS No. 107-06-2) are summarized below.

Chemical class	halogenated aliphatic hydrocarbon (purgeable halocarbons)
Molecular weight	98.98
Vapor pressure	64 mm Hg at 20°C (U.S. EPA, 1984)
Water solubility	8524 mg/ℓ at 20°C (Horvath, 1982)
Octanol/water partition coefficient	30.2 (Hansch and Leo, 1979)
Soil mobility (predicted as retardation factor for soil depth of 140 cm and organic carbon content of 0.087%)	1.2 (Wilson et al., 1981)
Bioconcentration factor (in bluegill, Lepomis macrochirus)	2 (U.S. EPA, 1980a)
Half-lives in:	
Air	36-127 days (U.S. EPA, 1984)
Water	4 hours (U.S. EPA, 1984)

The half-life of 4 hours for 1,2-dichloroethane in water is an estimated value under a wind speed of 3 m/sec, a water current of 1 m/sec and a water depth of 1 m. This half-life value is probably a lower limit for evaporation in water, since particulate material in natural water will retard the evaporation process.

A half-life of 1,2-dichloroethane in soil could not be located in the available literature; however, evaporation is expected to be the predominant loss mechanism from the soil surface. The half-life for soil evaporation should be longer than its evaporation half-life from water (Wilson et al.,

1981). In subsurface soil, biodegradation and other chemical degradation of 1,2-dichloroethane is likely to be slow (U.S. EPA, 1984; Wilson et al., 1981). Therefore, 1,2-dichloroethane is expected to transport downward through soils, especially through soils with low organic matter content.

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL MAMMALS

2.1. ORAL

Pertinent data regarding oral absorption of 1,2-dichloroethane in humans could not be located in the available literature, but numerous reports of accidental or suicidal ingestion of the chemical indicate very high absorption (NIOSH, 1976).

Very high absorption of 1,2-dichloroethane has been demonstrated clearly in laboratory animals. Reitz et al. (1982) administered 150 mg ^{14}C-1,2-dichloroethane/kg bw in corn oil to rats. Recovery of radioactivity in exhaled air, urine and carcass at the end of 48 hours was virtually complete. Spreafico et al. (1978, 1979, 1980) administered 25, 50 or 150 mg 1,2-dichloroethane/kg bw in corn oil by gavage to rats. Absorption was rapid, with peak blood levels occurring within 20 minutes. Peak blood levels appeared to be linearly related to dose level, although tissue levels did not, which the authors interpreted to suggest passive transport across the GI tract.

Spreafico et al. (1978, 1979, 1980) also derived rate constants for absorption by rats at each dose level. They observed a markedly lower rate constant for the highest (150 mg/kg) dose. At the lowest dose given (25 mg/kg), one-half the dose was absorbed from the GI tract by 3.3 minutes, and at the highest dose (150 mg/kg), one-half the dose was absorbed by 6.4 minutes. When the rate of absorption of 25 and 50 mg 1,2-dichloroethane/kg was determined with water vehicle, it was found that absorption was more rapid than with corn oil vehicle (k_a in water = 0.299, k_a in oil = 0.209 for 25 mg/kg dose). Withey et al. (1982) further investigated the effect of vehicle on absorption rate of 1,2-dichloroethane by administering 100 mg/kg bw in water or corn oil to fasted rats. The post absorptive peak

blood concentration was ~5-fold higher with water vehicle (84.6 μg/mℓ) compared with corn oil vehicle (15.9 μg/mℓ). Furthermore, peak blood concentrations were reached 3 times more quickly with water vehicle (3.2 minutes) compared with corn oil vehicle (10.6 minutes).

2.2. INHALATION

Absorption of inhaled 1,2-dichloroethane in man has not been quantitated, but the fact that the chemical has a moderately high (80 mm Hg at 25°C) vapor pressure and a high blood/air partition coefficient (19.5) (Sato and Nakajima, 1979) suggests rapid and complete pulmonary absorption.

Urusova (1953) reported that women exposed to ~15.5 ppm 1,2-dichloroethane in air during a normal workday accumulated the chemical in breast milk. Initial concentrations in exhaled air following exposure were 14.5 ppm, indicative that the women absorbed 1,2-dichloroethane through their lungs and reached blood and total body equilibrium with inspired air within the daily work period.

Reitz et al. (1980, 1982) exposed four Osborne-Mendel rats to 150 ppm 1,2-dichloroethane for 6 hours. Equilibrium in blood was reached in ≈1 hour and was maintained at ~9 μg/mℓ. Upon termination of exposure, blood levels fell rapidly, approaching 0 in about 1.5 hours. Spreafico et al. (1980) exposed rats to atmospheric concentrations of 50 or 250 ppm 1,2-dichloroethane for 6 hours. Blood equilibria were reached at ~2 and ~3 hours, respectively, for low- and high-dose groups. Blood levels attained by high-dose group rats (~29.36 μg/mℓ) were considerably higher than those attained by low-dose group rats (1.34 μg/mℓ).

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. Reports of subchronic oral exposure of humans to 1,2-dichloroethane could not be located in the available literature. Only one bioassay involving subchronic animal oral exposure to 1,2-dichloroethane was located. Munson et al. (1982) exposed male CD-1 mice to three concentrations of 1,2-dichloroethane in drinking water. The calculated TWA doses consumed based on measured water consumption were 3, 24 and 189 mg/kg bw/day for a 90-day exposure period. Concurrent with this study, mice were exposed to 4.9 or 49 mg/kg bw/day by gavage for 14 days. Total numbers of mice in each group were not specified. Exposure to 1,2-dichloroethane in the 14-day study did not affect body weight; 90-day exposure in drinking water elicited a dose-dependent decrease in growth rate and water consumption. Body weights were recorded for 32 mice in each group in the 90-day trial, but an unspecified number were weighed in the 14-day trial. At the termination of either study, organ weights (liver, spleen, lung, thymus, kidney, brain) were not affected by treatment. Hematologic parameters were evaluated in 10-12 and 16 mice/dose group in the 14- and 90-day studies, respectively. Hematologic parameters were unaltered by treatment, with the exception that exposure to 49 mg/kg/day 1,2-dichloroethane by gavage for 14 days depressed leukocyte counts ~30%. Leukocyte counts remained normal in drinking water-exposed rats at the end of 90 days.

The status of the humoral immune system was evaluated by measuring the number of antibody-forming cells to SRBC after 14 and 90 days, the serum antibody level to SRBC after 90 days and the lymphocyte response to lipopolysaccharide from Salmonella typhosa 0901 after 90 days (Munson et al., 1982). Evaluation of 10-12 mice/group in the 14-day study showed that

1,2-dichloroethane reduced ($p<0.05$) the number of antibody-forming cells in both low- and high-dose groups. Mice in the 90-day study showed no significant reduction in antibody-forming cells, nor did they show a significant response in hemagglutination titer or spleen cell response to lipopolysaccharide. Cell-mediated immunity, evaluated by measuring the delayed hypersensitivity reaction to sheep erythrocytes and the response to the T-lymphocyte mitogen, concanavalin A, revealed a significant ($p<0.05$) inhibition in both 14-day groups but no inhibition in the 90-day groups. These investigators observed immunosuppression in the 14-day gavage-exposed mice but no significant immunosuppression in the 90-day drinking water-exposed mice. They suggested that bolus administration of 1,2-dichloroethane may have resulted in a higher effective dose at the immunoresponsive site than did administration through the drinking water. A second explanation offered was that over a period of time 1,2-dichloroethane may induce its own metabolism, reducing its concentration at the effective site.

3.1.2. Inhalation. Reports of repeated exposure of humans to 1,2-dichloroethane are in Section 3.2.2., regarding chronic inhalation exposure.

Several investigators have subjected numerous species of animals to inhalation exposure of 1,2-dichloroethane for various lengths of time. Spencer et al. (1951) exposed monkeys, rats, guinea pigs and rabbits to 100 ppm (405 mg/m^3) or 400 ppm (1620 mg/m^3) 1,2-dichloroethane for periods ranging from ~24-36 weeks. Exposure was 7 hours/day, 5 days/week. Additionally, rats and guinea pigs were exposed to 200 ppm (810 mg/m^3) for ~30 and 36 weeks, respectively. Concentrations of 400 ppm 1,2-dichloroethane in air resulted in mortality in monkeys (2/2), guinea pigs (16/16) and rats (30/30) within 2-40 exposures. A group of three rabbits exposed to

400 ppm for 165 exposures (33 weeks) evidenced no effect on general appearance, body weight, histology of selected organs, hematologic parameters or blood chemistries; rabbits were clearly the most resistant species tested. Administration of 200 ppm 1,2-dichloroethane for 151 exposures was associated with no adverse effects on general appearance, behavior, growth, final body or organ weights or gross or histologic pathology in 30 rats. Guinea pigs (16) exposed to 200 ppm for 180 exposures evidenced reduced growth, reduced final body weights, and hepatomegaly (males only) and hepatic degeneration in both sexes. Guinea pigs appeared to be more sensitive to 1,2-dichloroethane than did rats in this study. Exposure of rats, guinea pigs, rabbits and monkeys to 100 ppm 1,2-dichloroethane for 121-178 exposures resulted in no adverse effects on general behavior, appearance, growth, mortality, final body or organ weights, gross or microscopic pathology, selected hematologic parameters or blood chemistries. In this study, 100 ppm 1,2-dichloroethane defined a NOEL in all four species tested.

Heppel et al. (1946) demonstrated heavy mortality in rabbits (5/5), guinea pigs (14/20) and rats (16/16) exposed to 400 ppm 1,2-dichloroethane after 4 (rats), 45 (guinea pigs) or 97 (rabbits) exposures of 7 hours/day, 5 days/week. Male puppies (3) or adult female dogs (6) experienced no mortality and only slight fatty degeneration of the liver when exposed to 400 ppm 1,2-dichloroethane for 167-177 exposures. Spencer et al. (1951) demonstrated no mortality in rats or guinea pigs exposed to 200 ppm 1,2-dichloroethane for >151 exposures; however, Heppel et al. (1946) noted heavy mortality in rats (7/12), guinea pigs (5/14) and mice (18/20) after 44, 88 or 7 exposures, respectively, to 200 ppm in air. Exposure to 100 ppm 1,2-dichloroethane for 4 months resulted in no adverse effects in 39 rats or 16 guinea pigs. Furthermore, 15/16 female rats became pregnant and rat pups

were apparently unaffected by exposure. In this study, 100 ppm also appeared to define a NOEL.

Hofmann et al. (1971) exposed 10 rats, 10 guinea pigs, 4 rabbits and 4 cats to 500 ppm 1,2-dichloroethane for 6 weeks or 100 ppm 1,2-dichloroethane for 17 weeks at 6 hours/day, 5 days/week. Exposure to 500 ppm resulted in mortality in all species except the cat, which showed cardiomegaly and elevated blood urea nitrogen. Exposure to 100 ppm for 17 weeks resulted in no clinical symptoms, no effects on selected blood chemistry parameters and no change in liver, kidney or other (unspecified) organs. Cats exposed to 100 ppm, however, reportedly did not grow as well as unexposed (control) cats. This study, therefore, appeared to define 100 ppm 1,2-dichloroethane as a LOAEL for subchronic inhalation exposure.

3.2. CHRONIC

3.2.1. Oral. Pertinent data regarding chronic oral exposure of humans to 1,2-dichloroethane could not be located in the available literature. Only one report of chronic oral exposure in laboratory animals, an NCI (1978) car- cinogenicity bioassay, was located in the available literature. Details of experimental protocol and results are given in Section 4.2. Groups of male and female Osborne-Mendel rats were treated by gavage with TWA doses of 95 or 47 mg/kg bw/day for 78 weeks and observed for an additional 28 weeks. Groups of male and female B6C3F_1 mice were treated by gavage with TWA doses of 195 or 97 mg/kg bw/day (male) or 299 or 149 mg/kg bw/day (female) for 78 weeks, followed by a 12-13 week observation period.

No significant dose-related body weight depression in rats of either sex was noted (NCI, 1978). Heavy mortality of treated rats occurred early in the study, particularly in the high dose groups. It appeared that toxic, rather than carcinogenic, effects of 1,2-dichloroethane were responsible for

the mortality. Mean body weight depression in high-dose female mice was noted as early as the 15th week of treatment. No significant dose-related mean body weight depression was observed in male mice or low-dose female mice. A significant positive association between increased dosage and elevated mortality in female mice was determined. Between weeks 60 and 80, mortality accounted for 72% (36/50) of high dose females. The finding of one or more tumors in these mice suggested that these deaths may have been tumor-related. No significant relation between dose and mortality in male mice was found.

3.2.2. Inhalation. There are many reports of repeated occupational exposure to 1,2-dichloroethane, particularly in the foreign literature (primarily Russian, Polish and German). Information on duration and exposure levels is often poorly documented. Collectively, however, the reports present a fairly clear picture of the clinical syndrome associated with the toxicity of 1,2-dichloroethane in man. These reports are discussed thoroughly in U.S. EPA (1984); only a brief summary of the more relevant data, taken from U.S. EPA (1983a), will be presented here.

Repeated exposure to 1,2-dichloroethane vapor in the workplace has resulted in anorexia, nausea, vomiting, weakness and fatigue, nervousness, epigastric pain/discomfort, and irritation of the respiratory tract and eyes (McNally and Fostvedt, 1941; Siegel, 1947; Rosenbaum, 1947; Watrous, 1947; Rejsek and Rejskova, 1947; Delplace et al., 1962; Suveev and Babichenko, 1969). In one study (Suveev and Babichenko, 1969), examination of 12 symptomatic workers who were brought to a clinic revealed paleness and cold sweat (12/12), bradycardia (9/12), systolic murmur (5/12), diarrhea (5/12; 3/12 with blood) and enlarged livers that were soft and tender to palpation (9/12). Muffled heart sounds, increased rate of respiration, rales, and

coated and dry tongues were also observed, but incidences were not stated. Signs of nervous system dysfunction have also been reported in cases of chronically exposed workers. These include nystagmus, fine tongue tremors and sluggish patellar reflex (McNally and Fostvedt, 1941); encephalic disorders (Delplace et al., 1962); and decreased muscle tone, loss of reflexes, a positive Romberg's sign and deafness (Suveev and Babichenko, 1969). Complaints of hand and arm eczema that appeared within the first year of exposure were recorded in 11/16 cases by Delplace et al. (1962). Exposure concentrations and information on the types of exposures were not provided in any of the reports cited above.

Kozik (1957) reported the results of a health and morbidity survey of Russian aircraft industry workers. All of the workers in the study group (size not stated) were employed in a shop where glue that contained 1,2-dichloroethane as a solvent was used to bond rubber sheets to metal forms in a soft tank fabrication process. Most of these workers were gluers, but a small number worked inside the completed tanks to disassemble the forms. The chemical was emitted to the air during application and glue drying.

According to Kozik (1957), ~500 atmospheric measurements of 1,2-dichloroethane were taken. Although the sampling and analytical methods were not mentioned, NIOSH (1976) felt that the data were presented in sufficient detail to permit estimations of TWA exposures. NIOSH (1976) estimated that 44-46% of the total exposure occurred during the gluing operations, when the TWA concentrations were ~28 ppm during application and ~16 ppm when the glue was drying. When other operations were performed in the same shop (during the second half of the workshift), the TWA concentration was ~11 ppm. The TWA for the total shift was estimated to be 15 ppm. Concentrations ranged from ~4-50 ppm; concentrations >20 ppm were associated only

with the gluing and drying operations and occurred ~15% of the time. NIOSH (1976) noted, however, that the aforementioned TWA concentrations may be an overestimate of most of the workers' exposure for several reasons. First, the tabulation of measurements in the glue application category also contained high values (45-52 ppm) that were experienced only by an insignificant number of workers who disassembled the molds within the finished tanks. Second, the measurements were apparently not breathing zone measurements, and third, the ventilation system was designed with the exhaust ducts on the floor. Considering this information, NIOSH (1976) concluded that a more realistic estimation of the TWA exposure of the majority of the workers is 10-15 ppm.

Workers (total number not stated) who were engaged in the production of soft tanks during the years 1951-1955 experienced increased morbidity and lost workdays when compared with workers in the entire factory (Kozik, 1957). Disease categories examined included acute GI disorders, neuritis and reticulitis. An in-depth analysis of the morbidity rate with temporary disability for 1954-1955 showed high rates for GI diseases, liver and gall bladder diseases and diseases of the muscle, tendons and neuronal ganglia. The liver and gall bladder diseases were considered by Kozik (1957) to be related to a specific toxic effect of 1,2-dichloroethane (the dyspeptic symptoms it causes reportedly are often diagnosed as gastritis), but the diseases of the muscle, tendon and ganglia were associated with the numerous repetitive motions the workers had to make when applying the glue. Further examination of 83 of the gluers revealed diseases of the liver and bile ducts (19/83), neurotic conditions (13/83), autonomic dystonia (11/83), asthenic conditions (5/83) and goiter and hyperthyroidism (10/83).

Visual-motor reactions were studied at the beginning and end of 14 workdays in 17 of the gluers and 10 "control" machinists (Kozik, 1957). A device was used to determine simple and complex reaction (color differentiation) times, as well as reaction times in a modification of the complex reaction task, but details of the tests were not given. A comparison of the mean rates for all three reactions showed no significant differences in the two groups either before or after work. Nervous system dysfunction was suggested, however, by the results of the complicated reaction tests. "Most" of the gluers made errors in the complex "reaction" task, while the machinists made no errors. In the modified complex reaction test, errors were committed both before and after work by 15/17 gluers; 4/10 machinists made errors, but only at the end of the workday.

Chronic toxicity of inhalation of 1,2-dichloroethane in animals has been studied by two groups of investigators. Maltoni et al. (1980) exposed groups of 90 male and 90 female Sprague-Dawley rats and Swiss mice to levels of 0, 5, 10, 50 or 250 ppm 1,2-dichloroethane 7 hours/day, 5 days/week for 78 weeks. After several days of exposure, both rats and mice in the high dose (250 ppm) group evidenced "severe toxicity," and exposure was reduced to 150 ppm for the remainder of the study. Among the groups of rats, those exposed to 5 ppm 1,2-dichloroethane survived the longest. No dose-related trend in mortality was noted. Female mice in the high (250-150 ppm) dose groups had a lower survival rate than did mice in the other groups. No other parameters of toxicity were mentioned in this study, which was designed primarily as a carcinogenicity bioassay.

Spreafico et al. (1980) investigated the effects of inhalation of identical concentrations (0, 5, 10, 50 or 250-150 ppm) of 1,2-dichloroethane in air on hematologic and clinical chemistry parameters of 3- or 12-month-old

rats exposed for 3, 6, 12 or 18 months for 7 hours/day, 5 days/week. At least eight animals from each dosage group were examined at each time interval. The results suggested that 18 months of exposure to 150 ppm 1,2-dichloroethane resulted in no marked evidence of toxicity. There were no statistically significant differences between treated and control animals in circulating levels of red blood cells, white blood cells or differential count, platelets or total serum protein. Percentages of albumin and gamma globulin varied during the study, but the variation was apparently not dose-related. No significant treatment-related effects on serum levels of liver enzymes, bilirubin, cholesterol, glucose, uric acid or blood urea nitrogen were noted in rats exposed for 18 months. Rats exposed for 12 months were 14 months old when exposure began. They showed alteration in liver and kidney function, manifested by significantly altered levels of serum hepatic enzymes and uric acid. These changes did not appear to follow a dose-related pattern. No changes in hematologic parameters or urinalysis were noted. Histological examination was not a part of this study.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. No reports of teratogenicity in humans or animals orally exposed to 1,2-dichloroethane could be located in the available literature.

3.3.2. Inhalation. No reports of teratogenicity in humans associated with inhalation of 1,2-dichloroethane could be located in the available literature.

The ability of 1,2-dichloroethane to cause adverse reproductive or fetal developmental effects cannot be fully assessed, since few investigators have adequately studied these effects. Several Russian studies report adverse effects such as lengthened estrus cycle, change in duration of various phases of the estrus cycle, decreased percentage of live births, decreased

fetal weight at delivery and decreased weight gain after birth. Unfortunately, these reports do not present the original data; various techniques and tests are mentioned but results are not included, details of analytical procedures are lacking, and insufficient information is given to support the authors conclusions. These studies will not be reviewed here.

Rao et al. (1980) reported on a Dow Chemical Company teratogenicity study in rats and rabbits. Groups of 16-30 rats and 19-21 rabbits were exposed to 100 or 300 ppm 1,2-dichloroethane for 7 hours/day. Rats were exposed on days 6-15 of gestation, and rabbits were exposed on days 6-18 of gestation. Rats and rabbits were sacrificed on days 21 and 29, respectively, and the dams were examined for pregnancy.

Signs of maternal toxicity, lethargy, ataxia, decreased body weight and decreased food consumption were noted in rats exposed to 300 ppm 1,2-dichloroethane. Rats exposed to 100 ppm 1,2-dichloroethane had no signs of maternal toxicity and, in fact, gained statistically more weight than the controls. No live offspring were found in rats exposed to 300 ppm 1,2-dichloroethane. No signs of fetal toxicity and no statistically significant increase in the incidence of terata were found in fetuses of rats exposed to 100 ppm 1,2-dichloroethane or in the fetuses from rabbits exposed to either 100 or 300 ppm 1,2-dichloroethane. These authors concluded that 1,2-dichloroethane was not teratogenic at the dosages tested in rats or rabbits, but that fetal toxicity occurred concomitantly with maternal toxicity in rats exposed to 300 ppm 1,2-dichloroethane.

Because the concentration of 1,2-dichloroethane associated in this study with fetal toxicity (300 ppm, ~1200 mg/m^3) was considerably higher than the level that Hofmann et al. (1971) found to result in reduced growth rate

in cats (100 ppm, ~405 mg/m³), this study (Rao et al., 1980) will not affect risk assessment.

3.4. TOXICANT INTERACTIONS

Heppel et al. (1945, 1946, 1947) produced high mortality (35%) in rats given 1.3 g 1,2-dichloroethane/kg bw orally. Pre- or postadministration of methionine, cysteine or other sulfhydryl-containing compounds markedly reduced mortality, presumably because these compounds enable the body to restore levels of glutathione reduced by metabolism of 1,2-dichloroethane (Johnson, 1965, 1966, 1967).

4. CARCINOGENICITY

4.1. HUMAN DATA

No case reports or epidemiologic studies of human carcinogenicity related to 1,2-dichloroethane were located in the available literature.

4.2. BIOASSAYS

4.2.1. Oral. Only one study, sponsored by the NCI (1978), examined the carcinogenicity of orally administered 1,2-dichloroethane in laboratory rodents. Osborne-Mendel rats were divided into high- and low-dose groups containing 50 rats of each sex. Untreated and vehicle control groups contained 20 rats of each sex. In the same study, similar numbers of B6C3F$_1$ mice were subjected to the same protocol. 1,2-Dichloroethane in corn oil was administered by gavage according to the schedules in Table 4-1 (for rats) and Table 4-2 (for mice). Inappropriate selection of initial doses resulted in early signs of toxicity, which necessitated numerous readjustments in dosage levels administered to both rats and mice. The final TWA dosages for male and female rats were 95 and 47 mg/kg bw/day; for male mice, 195 and 97 mg/kg bw/day; and for female mice, 299 and 149 mg/kg bw/day for high dose and low dose groups, respectively.

Early mortality was high in treated rats, particularly those in the high-dose group. Mortality was due to a number of causes, including bronchopneumonia and endocardial thrombosis. Terminal survival data in rats are presented in Table 4-3. Tumor incidences in rats and statistical significance are summarized in Table 4-4 (males) and Table 4-5 (females). Terminal survival data in mice are presented in Table 4-6. In male mice, mortality did not appear to be dose-related because mortality was considerably higher in the low-dose than in the high-dose group. The opposite trend

TABLE 4-1

Design Summary for 1,2-Dichloroethane Gavage Experiment in Osborne-Mendel Rats[a]

Group	Initial Number of Animals	1,2-Dichloroethane Dosage[b]	Observation Period		TWA Dosage Over a 78-Week Period[c]
			Treated (weeks)	Untreated (weeks)	
MALES					
Untreated control	20	NA	NA	106	NA
Vehicle control	20	0	78	32	0
Low-dose	50	50	7	NA	47
		75	10	NA	NA
		50	18	NA	NA
		50[d]	34	9	NA
		0	NA	32	NA
High-dose[e]	50	100	7	NA	95
		150	10	NA	NA
		100	18	NA	NA
		100[d]	34	9	NA
		0	NA	23	NA
FEMALES					
Untreated control	20	NA	NA	106	NA
Vehicle control	20	0	78	32	0

TABLE 4-1 (cont.)

Group	Initial Number of Animals	1,2-Dichloroethane Dosage[b]	Observation Period		TWA Dosage Over a 78-Week Period[c]
			Treated (weeks)	Untreated (weeks)	
Low-dose	50	50	7	NA	47
		75	10	NA	NA
		50	18	NA	NA
		50[d]	34	9	NA
		0	NA	32	NA
High-dose[e]	50	100	7	NA	95
		150	10	NA	NA
		100	18	NA	NA
		100[d]	34	9	NA
		0	NA	15	NA

[a]Source: NCI, 1978

[b]Dosage, given in mg/kg bw, was administered by gavage 5 consecutive days/week.

[c]TWA dosage = $\frac{\text{(dosage x weeks received)}}{\text{78 weeks}}$

[d]These dosages were cyclically administered with a pattern of 1 dosage-free week followed by 4 weeks (5 days/week) of dosage at the level indicated.

[e]All animals in this group died before the bioassay was terminated.

NA = Not applicable

TABLE 4-2

Design Summary for 1,2-Dichloroethane Gavage Experiment in B6C3F$_1$ Mice[a]

Group	Initial Number of Animals	1,2-Dichloroethane Dosage[b]	Observation Period		TWA Dosage[c]
			Treated (weeks)	Untreated (weeks)	
MALES					
Untreated control	20	NA	NA	90	NA
Vehicle control	20	0	78	12	0
Low-dose	50	75	8	NA	97
		100	70	NA	NA
		0	NA	12	NA
High-dose	50	150	8	NA	195
		200	70	NA	NA
		0	NA	13	NA

TABLE 4-2 (cont.)

Group	Initial Number of Animals	1,2-Dichloroethane Dosage[b]	Observation Period		TWA Dosage[c]
			Treated (weeks)	Untreated (weeks)	
FEMALES					
Untreated control	20	NA	NA	91	NA
Vehicle control	20	0	78	32	0
Low-dose	50	125	8	NA	149
		400	3	NA	NA
		150	67	NA	NA
		0	NA	13	NA
High-dose	50	250	8	NA	299
		400	3	NA	NA
		300	67	NA	NA
		0	NA	13	NA

[a]Adapted from NCI, 1978

[b]Dosage, given in mg/kg bw, was administered by gavage 5 consecutive days/week.

[c]TWA dosage = $\frac{\text{(dosage x weeks received)}}{\text{weeks receiving chemical}}$

NA = Not applicable

TABLE 4-3

Terminal Survival of Osborne-Mendel Rats Treated With 1,2-Dichloroethane (EDC)[a]

Group	Males		Females	
	Weeks in Study	Animals Alive at End of Study	Weeks in Study	Animals Alive at End of Study
Untreated control	106	4/20[b] (20%)	106	13/20[b] (65%)
Vehicle control	110	4/10 (20%)	110	8/20 (40%)
Low-dose	110	1/50 (2%)	101	1/50 (2%)
High-dose	101	0/50[c] (0%)	93	0/50[c] (0%)

[a]Source: Adapted from NCI, 1978

[b]Five rats were sacrificed at 75 weeks.

[c]All animals in this group died before the bioassay was terminated.

TABLE 4-4

Tumor Incidence and Statistical Significance in Male Osborne-Mendel Rats[a]

Exposure Route	Dose or Exposure	Duration of Treatment	Duration of Study	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (p value)[b]
Gavage	95 mg/kg[c]	78 weeks	101 weeks	≥99%[d]	corn oil	forestomach	squamous cell carcinoma	9/50 (p=0.007)[e]
						circulatory system	hemangiosarcoma	7/50 (p=0.016)[e]
						subcutaneous tissue	fibroma	6/50 (p=0.001)[e] (p=0.039)[f]
Gavage	47 mg/kg[c]	78 weeks	110 weeks	≥99%[d]	corn oil	forestomach	squamous cell carcinoma	3/50 (NS)
						circulatory system	hemangiosarcoma	9/50 (p=0.003)[e] (p=0.039)[f]
						subcutaneous tissue	fibroma	5/50 (p=0.017)[e]
Gavage	0 mg/kg/day (matched vehicle control)	78 weeks	110 weeks	NA	corn oil	forestomach	squamous cell carcinoma	0/20 (p=0.010)
						circulatory system	hemangiosarcoma	0/20 (NS)
						subcutaneous tissue	fibroma	0/20 (NS)
Gavage	0 mg/kg/day (pooled vehicle control)[g]	≥52 weeks	≥52 weeks	NA	corn oil	forestomach	squamous cell carcinoma	0/60 (p=0.001)
						circulatory system	hemangiosarcoma	1/60 (p=0.021)
						subcutaneous tissue	fibroma	0/60 (p=0.10)

[a]Source: NCI, 1978

[b]The probability levels for the Fischer exact test and the Cochran-Armitage test are given beneath the incidence of tumors in the treated and control groups, respectively, when $p<0.05$; otherwise, not significant (NS) is indicated.

[c]TWA dose reflecting gavage treatment 5 consecutive days/week for 78 weeks.

[d]Purity of >90% was reported by NCI (1978). Reanalysis indicated a purity of >99% (Hooper et al., 1980).

[e]Comparison with pooled control group

[f]Comparison with matched control group

[g]Pooled control group consisted of matched controls from bioassays of 1,2-dichloroethane, 1,1,2-trichloroethane and trichloroethylene.

NA = Not applicable

TABLE 4-5

Tumor Incidence and Statistical Significance in Female Osborne-Mendel Rats[a]

Exposure Route	Dose or Exposure	Duration of Treatment	Duration of Study	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (p value)[b]
Gavage	95 mg/kg[c]	78 weeks	93 weeks	≥99%[d]	corn oil	mammary gland	adenocarcinoma NOS	18/50 (p<0.001)[e] (p=0.002)[f]
						mammary gland	adenocarcinoma NOS or fibroadenoma	24/50 (p<0.001)[e,f]
Gavage	47 mg/kg[c]	78 weeks	110 weeks	≥99%[d]	corn oil	mammary gland	adenocarcinoma NOS	1/50 (NS)
						mammary gland	adenocarcinoma NOS or fibroadenoma	15/50 (p=0.009)[e] (p=0.003)[f]
Gavage	0 mg/kg (pooled vehicle control)[g]	≥52 weeks	≥52 weeks	NA	corn oil	mammary gland	adenocarcinoma NOS	1/59 (p<0.001)
						mammary gland	adenocarcinoma NOS or fibroadenoma	6/59 (p<0.001)

[a]Source: NCI, 1978

[b]The probability levels for the Fischer exact test and the Cochran-Armitage test are given beneath the incidence of tumors in the treated and control groups, respectively, when p<0.05; otherwise, not significant (NS) is indicated.

[c]TWA dose reflecting gavage treatment 5 consecutive days/week for 78 weeks.

[d]Purity of >90% was reported by NCI (1978). Reanalysis indicated a purity of ≥99% (Hooper et al., 1980).

[e]Comparison with pooled control group

[f]Comparison with matched control group

[g]Pooled control group consisted of matched controls from bioassays of 1,2-dichloroethane, 1,1,2-trichloroethane and trichloroethylene.

NA = Not applicable; NOS = Not otherwise specified

TABLE 4-6

Terminal Survival of B6C3F$_1$ Mice Treated With 1,2-Dichloroethane*

Group	Males		Females	
	Weeks in Study	Animals Alive at End of Study	Weeks in Study	Animals Alive at End of Study
Untreated control	90	7/20 (35%)	90	16/20 (80%)
Vehicle control	90	11/20 (55%)	90	16/20 (80%)
Low-dose	90	11/50 (22%)	91	34/50 (68%)
High-dose	91	21/50 (42%)	91	1/50 (2%)

*Source: Adapted from NCI, 1978

was noted for female mice. The incidences and statistical significance of tumor development in mice are summarized in Tables 4-7 (males) and 4-8 (females).

As detailed in the tables, male rats in the high-dose group experienced a significant increase in the incidence of squamous cell carcinomas of the forestomach, hemangiosarcoma and subcutaneous tissue fibroma, compared with controls. The incidence of all these tumors except squamous cell carcinoma of the forestomach was also statistically significant in the low-dose group, compared with controls. Mammary adenocarcinoma in female rats occurred at a significantly higher incidence in both treatment groups; mammary adenocarcinoma or fibroma occurred at significantly higher incidence in the high-dose group only when compared with controls. Both male and female mice showed significantly increased incidences of pulmonary alveolar/bronchiolar adenoma at both dosage levels. Male mice also had significantly increased incidences of hepatocellular carcinoma, but this effect was noted only in the high-dose group when compared with controls. Female mice had significantly increased incidences of mammary adenocarcinomas and endometrial stromal polyp or sarcoma in both the high-dose and low-dose groups, compared with controls. In this bioassay, 1,2-dichloroethane was carcinogenic in both male and female rats and mice.

4.2.2. Inhalation. Maltoni et al. (1980) exposed groups of 90 male and 90 female Sprague-Dawley rats to 0, 5, 10, 50 or 250 ppm 1,2-dichloroethane in inhaled air for 7 hours/day, 5 days/week for 78 weeks and observed them until spontaneous death. After several days of exposure, the 250 ppm group exhibited severe toxic effects, and the level of 1,2-dichloroethane was reduced to 150 ppm for the duration of the 78-week exposure period. Mortality varied among groups and a dose response relationship for mortality

TABLE 4-7

Tumor Incidence and Statistical Significance in Male B6C3F$_1$ Mice[a]

Exposure Route	Dose or Exposure	Duration of Treatment	Duration of Study	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (p value)[b]
Gavage	195 mg/kg[c]	78 weeks	91 weeks	≥99%[d]	corn oil	lung	alveolar/bronchiolar adenoma	15/48 (p<0.001)[e] (p=0.003)[f]
Gavage	97 mg/kg[c]	78 weeks	90 weeks	≥99%[d]	corn oil	lung	alveolar/bronchiolar adenoma	1/47 (NS)
						liver	hepatocellular carcinoma	6/47 (NS)
Gavage	0 mg/kg (matched vehicle controls)	78 weeks	90 weeks	NA	corn oil	lung	alveolar/bronchiolar adenoma	0/19 (p<0.001)
						liver	hepatocellular carcinoma	1/19 (p=0.025)
Gavage	0 mg/kg (pooled vehicle controls)[g]	≥52 weeks	≥52 weeks	NA	corn oil	lung	alveolar/bronchiolar adenoma	0/59 (p<0.001)
						liver	hepatocellular carcinoma	4/59 (p=0.006)

[a]Source: NCI, 1978

[b]The probability levels for the Fischer exact test and the Cochran-Armitage test are given beneath the incidence of tumors in the treated and control groups, respectively, when p<0.05; otherwise, not significant (NS) is indicated.

[c]TWA dose reflecting gavage treatment 5 consecutive days/week for 78 weeks.

[d]Purity of >90% was reported by NCI (1978). Reanalysis indicated a purity of >99% (Hooper et al., 1980).

[e]Comparison with pooled control group

[f]Comparison with matched control group

[g]Pooled control group consisted of matched controls from bioassays of 1,2-dichloroethane, 1,1,2-trichloroethane and trichloroethylene.

NA = Not applicable

TABLE 4-8

Tumor Incidence and Statistical Significance in Female B6C3F$_1$ Mice[a]

Exposure Route	Dose or Exposure	Duration of Treatment	Duration of Study	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (p value)[b]
Gavage	299 mg/kg[c]	78 weeks	91 weeks	≥99%[d]	corn oil	lung	alveolar/bronchiolar adenoma	15/48 (p<0.001)[e] (p=0.006)[f]
						mammary gland	adenocarcinoma	7/48 (p=0.003)[e]
						uterus	endometrial stromal polyp or sarcoma	5/47 (p=0.014)[e]
Gavage	149 mg/kg[c]	78 weeks	91 weeks	≥99%[d]	corn oil	lung	alveolar/bronchiolar adenoma	7/50 (p=0.046)[e]
						mammary gland	adenocarcinoma	9/50 (p=0.001)[e] (p=0.039)[f]
						uterus	endometrial stromal polyp or sarcoma	5/49 (p=0.016)
Gavage	0 mg/kg (matched vehicle controls)	78 weeks	90 weeks	NA	corn oil	lung	alveolar/bronchiolar adenoma	1/20 (p=0.005)
						mammary gland	adenocarcinoma	0/20 (NS)
						uterus	endometrial stromal polyp or sarcoma	0/20 (NS)
Gavage	0 mg/kg (pooled vehicle controls)[g]	≥52 weeks	≥52 weeks	NA	corn oil	lung	alveolar/bronchiolar adenoma	2/60 p<0.001
						mammary gland	adenocarcinoma	0/60 (p=0.007)
						uterus	endometrial stromal polyp or sarcoma	0/60 (p=0.017)

[a]Source: NCI, 1978

[b]The probability levels for the Fischer exact test and the Cochran-Armitage test are given beneath the incidence of tumors in the treated and control groups, respectively, when p<0.05; otherwise, not significant (NS) is indicated.

[c]TWA dose reflecting gavage treatment 5 consecutive days/week for 78 weeks.

[d]Purity of >90% was reported by NCI (1978). Reanalysis indicated a purity of ≥99% (Hooper et al., 1980).

[e]Comparison with pooled control group

[f]Comparison with matched control group

[g]Pooled control group consisted of matched controls from bioassays of 1,2-dichloroethane, 1,1,2-trichloroethane and trichloroethylene.

NA - Not applicable

was not apparent. The low-dose (5 ppm) groups had the greatest number of survivals at the end of 52 weeks of exposure. The incidences of tumors found upon necropsy were low and not related to exposure to 1,2-dichloroethane. Several groups of female rats showed a considerable incidence of benign mammary fibromas and fibroadenomas, but the incidence appeared to be related to survival (age) rather than directly to treatment.

An identical protocol was used to expose groups of 90 male and 90 female Swiss mice to 1,2-dichloroethane (Maltoni et al., 1980). Mice also exhibited signs of severe toxicity to 250 ppm 1,2-dichloroethane after several days of exposure, and the concentration was reduced to 150 ppm for the duration of the 78-week treatment period. At 52 and 78 weeks, overall survival rates were 82.4 and 45.9%, respectively. Survival of high-dose (250-150 ppm) female mice was slightly reduced. Tumor development among treatment and control groups was low and not statistically related to treatment.

An earlier study by Spencer et al. (1951) failed to demonstrate carcinogenicity of 1,2-dichloroethane in 15 male and 15 female Wistar rats given 151 exposures at 200 ppm for 7 hours duration over a 212-day period.

4.3. OTHER RELEVANT DATA

Many investigators have tested 1,2-dichloroethane for mutagenicity in microorganisms, mammalian cells *in vitro* and rodents *in vivo*. Most of the investigations in bacteria indicated that 1,2-dichloroethane was weakly mutagenic. Metabolic activation with rat hepatic S-9 fraction increased the strength of the response, indicating that metabolites may be more potent mutagens. Studies that typify this phenomenon are summarized in Table 4-9. King et al. (1979) observed negative results in five strains of *Salmonella typhimurium*. Excessive evaporation from the culture plates may have contributed to these negative results.

TABLE 4-9

Mutagenicity of 1,2-Dichloroethane in *Salmonella typhimurium* Assay

Test System	Strains	Activation System	Chemical Information	Results	Reference
Salmonella/microsome assay (vapor exposure)	TA1535 TA100 TA1538 TA98	PCB-induced rat liver S-9 mix	concentrations tested: up to 231.8 µmol/plate at determined by GLC analysis of distilled water samples.	Negative in standard plate test. Positive in desiccator testing in strains TA1535 and TA100.	Barber et al., 1981
Salmonella/microsome assay (plate test)	TA1535	S-9 mix from livers of un-induced male R strain Wistar rats plus NADPH generating system	concentration tested: up to 45 µmol/plate	Positive response (2-fold increase without activation; nearly 10-fold increase with activation). Negative controls yielded roughly 15 revertants/ plates.	Rannug and Ramel, 1977
Salmonella/microsome assay (plate test)	TA1535 TA100 TA1537 TA1538	PCB-induced rat liver S-9	concentration tested: 36 µmol/plate	Negative	King et al., 1979
Escherichia coli K 12/343/113 (suspension test)	TA98		10 mM (suspension assay) 2 mM/kg i.p. injection female NMRI mice	Negative Negative	

The ability of 1,2-dichloroethane to cause mutations in Drosophila melanogaster has also been investigated. Sex-linked recessive lethal mutations in D. melanogaster have been produced by concentrations of 50 mM solutions of 1,2-dichloroethane in 5% sucrose fed to 1- to 2-day-old males (King et al., 1979) and by exposure of 3-day-old virgin females to 700 ppm in air for 4-6 hours (Shakarnis, 1969, 1970). Nylander et al. (1979) induced somatic cell mutations in D. melanogaster with 0.1% 1,2-dichloroethane in food given during larval development.

Tan and Hsie (1981) showed a dose-related increase in mutations in cultured Chinese hamster ovary cells exposed to 1,2-dichloroethane. Metabolic activation with rat hepatic S-9 fraction increased response about 4-fold.

Shakarnis (1969) suggested that 1,2-dichloroethane may cause chromosomal aberrations in D. melanogaster. This investigator exposed virgin females to 700 ppm 1,2-dichloroethane for 4-6 hours and observed a significantly ($p<0.05$) greater incidence of exceptional F_1 offspring, indicative of meiotic nondisjunction.

Both King et al. (1979) and Jenssen and Ramel (1980) reported negative results in the micronucleus test in mouse bone marrow smears.

4.4. WEIGHT OF EVIDENCE

As discussed previously in Section 4.2., the NCI (1978) gavage bioassay clearly demonstrated that 1,2-dichloroethane was carcinogenic to both rats and mice. Treated male rats exhibited significantly increased incidences of squamous cell carcinomas of the forestomach, hemangiosarcomas and benign subcutaneous tissue fibromas, compared with controls. Treated female rats experienced a significantly increased incidence of mammary adenocarcinomas, compared with controls. Both male and female mice experienced significantly increased incidences of pulmonary alveolar/bronchiolar adenomas in treatment

groups, compared with controls. Treated male mice also experienced a significantly increased incidence of hepatocellular carcinomas, and treated female mice experienced increased incidences of mammary adenocarcinomas and endometrial tumors (both stromal polyps and sarcomas), compared with controls.

Chronic (440-594 days) application of 1,2-dichloroethane to the skin of mice was not associated with an increased incidence of skin tumors, but appeared to be related to an increased incidence of benign papilloma formation in the lungs (Van Duuren et al., 1979). Inhalation exposure to levels of up to 150-250 ppm 1,2-dichloroethane in rats and mice for 78 weeks failed to result in significantly increased incidences of tumors, compared with controls (Maltoni et al., 1980).

No relevant case reports or epidemiologic studies of human carcinogenicity of 1,2-dichloroethane could be located in the available literature.

Although no data exist regarding the carcinogenicity of 1,2-dichloroethane to humans, the evidence is clearly sufficient that the compound is a carcinogen in animals. Applying the criteria proposed by the Carcinogen Assessment Group of the U.S. EPA for evaluating weight of evidence for the carcinogenicity of 1,2-dichloroethane in humans (Federal Register, 1984), the compound is most appropriately classified as a Group B2 - Probable Human Carcinogen.

5. REGULATORY STANDARDS AND CRITERIA

Current criteria for 1,2-dichloroethane are summarized in Table 5-1. The ACGIH (1983) has recommended a TLV-TWA of 10 ppm (40 mg/m³) and a TLV-STEL of 15 ppm (60 mg/m³) for 1,2-dichloroethane. This TLV represents a reduction from a previously recommended level of 50 ppm, presumably based on the observations of numerous effects on the nervous systems and livers of Russian workers exposed to $\leq$16 ppm in air (ACGIH, 1980). NIOSH (1976) currently recommends an 8-hour TWA criterion of 1 ppm with a 2 ppm ceiling for short-term exposure. This represents a reduction from 5 ppm, which was recommended in 1978.

The U.S. EPA (1980a) has recommended a criterion for 1,2-dichloroethane in ambient water of 9.4 µg/ℓ, based on the NCI (1978) finding that the chemical is a carcinogen in laboratory animals.

TABLE 5-1

Current Regulatory Standards and Criteria

Location	Criterion or Standard	Reference
Workroom air:		
TLV-TWA	10 ppm (40 mg/m³)	ACGIH, 1983
TLV-STEL	15 ppm (60 mg/m³)	
TWA	1 ppm	NIOSH, 1976
STEL	2 ppm	
Ambient water	9.4 µg/ℓ	U.S. EPA, 1980a

6. RISK ASSESSMENT

6.1. ACCEPTABLE INTAKE SUBCHRONIC (AIS)

1,2-Dichloroethane is a known animal carcinogen and data are sufficient for computing a q_1^*. Therefore, it is inappropriate to calculate an oral or inhalation AIS for 1,2-dichloroethane.

6.2. ACCEPTABLE INTAKE CHRONIC (AIC)

1,2-Dichloroethane is a known animal carcinogen and data are sufficient for computing a q_1^*. Therefore, it is inappropriate to calculate an oral or inhalation AIC for 1,2-dichloroethane.

6.3. CARCINOGENIC POTENCY (q_1^*)

6.3.1. Oral Exposure. The U.S. EPA (1984) chose to base calculation of a q_1^* on the incidence of hemangiosarcomas in male rats in the NCI (1978) bioassay rather than on the incidence of hepatic carcinomas in male mice, because hemangiosarcomas in rats were considered to be more sensitive tumors at a site further removed from direct contact with the agent. Because of high mortality in the high-dose group, time-to-death data were used rather than data based on survival >50 weeks. A q_1^* of 6.9×10^{-2} mg/kg/day for human exposure was calculated. The Health Assessment Document on 1,2-dichlorothane (U.S. EPA, 1984) contains a complete discussion of the derivation of this q_1^*.

6.3.2. Inhalation Exposure. As discussion in Section 4.2.2., inhalation exposure to 1,2-dichloroethane failed to result in significant increases in tumor incidence in Sprague-Dawley rats or Swiss mice (Maltoni et al., 1980) or female Wistar rats (Spencer et al., 1951). No other reports of carcinogenicity of 1,2-dichloroethane by inhalation exposure were located in the available literature. Calculation of a q_1^* for 1,2-dichloroethane by inhalation exposure is, therefore, precluded.

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APPENDIX

Summary Table for 1,2-Dichloroethane

Carcinogenic Potency	Species	Experimental Dose/Exposure	Effect	q_1*	Reference
Inhalation				ND	
Oral	rat	47 mg/kg bw	hemangiosarcomas $(mg/kg/day)^{-1}$	6.9×10^{-2}	NCI, 1978 U.S. EPA, 1984

ND = Not derived